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Management of Infections Due to Antibiotic-Resistant *Streptococcus pneumoniae*

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INTRODUCTION 628
BACTERIAL MENINGITIS 628
Newer Agents for Treating Meningitis due to Antibiotic-Resistant *S. pneumoniae* 631
Dexamethasone 631
Repeat Lumbar Puncture 631
BACTEREMIA 631
PNEUMONIA 633
Implications 634
MISCELLANEOUS INFECTIONS 635
UPPER RESPIRATORY INFECTIONS 635
Implications 638
ANTIBIOTICS IN DEVELOPMENT 638
Streptogramins 638
Cephalosporins 638
Trinems 638
Glycopeptides 638
Fluoroquinolones 638
Oxazolidinones 640
Rifabutin 640
CONCLUSIONS 640
REFERENCES 640

INTRODUCTION

Streptococcus pneumoniae is one of the most common organisms causing upper respiratory, lower respiratory, and invasive infections in children and adults. Management of pneumococcal infections used to be relatively straightforward, and penicillin generally was the antibiotic of choice. However, the worldwide emergence of antibiotic resistance among *S. pneumoniae* isolates has changed this approach (7, 83). The rapid development and spread of penicillin resistance and multiple-antibiotic resistance have occurred as a result of multiple factors, but prior antibiotic use, young age, and day care attendance are the most commonly identified risk features (7, 78). The mechanisms and prevalence of antibiotic resistance for *S. pneumoniae* have been the subject of numerous reviews (7, 28, 83) and will not be discussed further. The management of infections due to antibiotic-resistant *S. pneumoniae* is the focus of this article. Since the degree of antibiotic resistance continues to change and increase, the approach to managing these infections must be modified in response to these changes. Furthermore, there is no general agreement among experts how to best treat all pneumococcal infections due to resistant strains, especially those outside the central nervous system.

In vitro susceptibility studies of the activity of antibiotics against resistant *S. pneumoniae*, animal models, case reports, and series of cases are the primary sources of data upon which treatment strategies are based. However, the interpretation of treatment failures may be complicated. For example, in patients with an underlying illness and thus predisposed to pneumococcal infection, is a poor clinical outcome related to treatment failure when repeat cultures are negative for *S. pneumoniae*, or is this the natural history of the infection? Unfortunately, no large clinical trials have been able to address this question. In addition, since two or more agents that are active against penicillin- and cephalosporin-resistant *S. pneumoniae* are often included in the initial empirical antibiotic regimen for a patient, the efficacy of a single agent, especially penicillin alone, cannot be assessed. Keeping all of these factors in mind, we have summarized what is known about the management and outcome of infections due to antibiotic-resistant *S. pneumoniae*. In this review, the 1997 MIC interpretive standards from the National Committee on Clinical Laboratory Standards are used to categorize pneumococcal isolates as susceptible, intermediate, or resistant to the antibiotics under discussion (102). These breakpoints for the parenteral beta-lactam agents are based primarily on clinical outcome data for pneumococcal meningitis. Higher breakpoints are appropriate for non-central nervous system infections, and revised breakpoints are being proposed based on the site of infection as well as pharmacokinetic/pharmacodynamic considerations.

BACTERIAL MENINGITIS

Several reports of treatment failures related to pneumococcal isolates with decreased susceptibility to penicillin were published in the 1970s (2, 59, 90, 101, 112). In these cases, pneumococci with penicillin MICs between 0.1 and 1.0 μg/ml were

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TABLE 1. Failure of broad-spectrum cephalosporins to treat pneumococcal meningitis[b]

Location	Age	Therapy (mg/kg/day)	MIC (μg/ml) of:			Reference
			Penicillin	Cefotaxime	Ceftriaxone	
United States						
San Diego	2.5 yr	Ceftriaxone (100)[a]	0.5	2	2	24
Memphis	13 mo	Cefotaxime (200)[a]	0.25	32	16	133
	13 mo	Cefuroxime (150)	4	8	8	133
	4 mo	Cefotaxime (200)	0.5	8	4	133
	11 mo	Cefotaxime	2	16	8	85
Dallas	9 mo	Ceftriaxone (80)	2	4	4	55
Indianapolis	28 mo	Ceftriaxone (90)[a]	4	2	2	81
Ann Arbor	6 mo	Cefotaxime (200)[a]	2	>2	>2	76
Providence	33 yr	Ceftriaxone (4 g)[a]	1.4	1.4	1.0	88
Rochester	53 yr	Cefotaxime (12 g)	4	2	ND[c]	107
Spain	6 yr	Cefotaxime (200) and chloramphenicol	2	2	ND	3
	19 mo	Penicillin (500,000 U) and cefotaxime (150) and chloramphenicol (100)	1	2	ND	12
	18 mo	Penicillin (500,000 U) and cefotaxime (200 and 300)	1	0.5	0.05	11
	29 yr	Cefotaxime (240)	1	1	ND	32
France	8.5 mo	Cefotaxime (200) and aminoglycoside	2	2	ND	69
	11 mo	Cefotaxime (200)[a] or amoxicillin (250) and netilmicin	4	2	ND	69

[a] Dexamethasone adjunctive therapy administered.
[b] Repeat CSF cultures positive for *S. pneumoniae* on treatment.
[c] ND, not determined.

associated with microbiologic and/or clinical treatment failures in patients with bacterial meningitis being administered penicillin. These cases led to the conclusion that penicillin at routine doses did not result in high enough levels in the cerebrospinal fluid (CSF) of patients with bacterial meningitis (peak, about 1.0 μg/ml) (6, 73) to reliably treat meningitis due to pneumococcal strains "relatively resistant" to penicillin. At that time, ampicillin and chloramphenicol were the standard empirical agents for suspected bacterial meningitis in children. Chloramphenicol was considered an acceptable alternative agent to complete therapy if a penicillin-resistant *S. pneumoniae* isolate was recovered, which at that time was still an infrequent occurrence.

By the mid 1980s, ceftriaxone or cefotaxime were typically recommended for empirical treatment of children with suspected bacterial meningitis (94). *S. pneumoniae* isolates were uniformly susceptible to these extended-spectrum cephalosporins. However, by the early 1990s, as penicillin-resistant pneumococcal isolates became more common throughout the world, treatment failures associated with cefotaxime or ceftriaxone administration for pneumococcal meningitis were reported (Table 1). In such cases, the cefotaxime or ceftriaxone MICs for the pneumococcal isolates were generally ≥2.0 μg/ml. These infected children did not improve on therapy, and repeat CSF culture remained positive after one or more days of treatment. Other investigators reported successful treatment with cefotaxime or ceftriaxone when the agents had MICs of 1.0 μg/ml for these isolates, a value now considered intermediate susceptibility (137). (Therapy failed in one adult infected with an *S. pneumoniae* isolate for which the cefotaxime MIC was 1.0 μg/ml [32].) There also was one case of a 12-month-old child with pneumococcal meningitis whose initial isolate had penicillin and ceftriaxone MICs of 0.12 and 0.06 μg/ml, respectively. After 10 days of treatment with both penicillin and cefotaxime, fever reappeared while the patient was still on therapy; a repeat CSF culture again grew *S. pneumoniae*, now with penicillin and cefotaxime MICs of >1.0 and 1.0 μg/ml, respectively. Thus, resistance to β-lactam antibiotics increased during treatment of this child (100). It is also possible that a resistant subpopulation was selected by antimicrobial therapy.

Friedland and Klugman (52) reported that children with pneumococcal meningitis due to penicillin-nonsusceptible isolates (most intermediate susceptibility) treated with chloramphenicol had serious neurologic deficits more frequently than did children with penicillin-susceptible strains who received benzylpenicillin. The penicillin-nonsusceptible isolates had increased chloramphenicol MBCs compared with the penicillin-susceptible isolates; this was probably associated with decreased bactericidal activity in the CSF. The authors recommended that chloramphenicol no longer be regarded as an alternative agent in treating meningitis due to *S. pneumoniae* nonsusceptible to penicillin.

Various management strategies for treating pneumococcal meningitis due to antibiotic-resistant strains have been evaluated in a rabbit model. Following inoculation of an *S. pneumoniae* strain resistant to ceftriaxone (MIC, 2 to 4 μg/ml), high doses of ceftriaxone did not lead to adequate killing and bactericidal activity in CSF (54). However, the combination of vancomycin plus ceftriaxone was synergistic and superior to vancomycin therapy alone. In contrast, meropenem, a new carbapenem approved for treatment of bacterial meningitis in children as well as adults, was not particularly active despite achieving peak concentrations in CSF that were eightfold greater than the MIC. When dexamethasone was administered initially just before antibiotic treatment, lower levels of vancomycin and ceftriaxone were achieved in CSF, which was associated with delayed clearance of bacteria (29, 114). In contrast, dexamethasone did not affect the penetration of rifampin into the CSF. From these studies, it was concluded that ceftriaxone and rifampin should be used together for bacterial meningitis if dexamethasone is administered for the first 2 to 4 days of therapy.

Many patients with pneumococcal meningitis due to strains

TABLE 2. Treatment of pneumococcal meningitis: modifications based on antibiotic susceptibilities

Penicillin MIC (μg/ml)	Cefotaxime/ ceftriaxone MIC (μg/ml)	Therapy	Dosage	
			Children[a]	Adults
<0.1	≤0.5	Penicillin	300,000–400,000 U every 4 or 6 h	300,000 U[a] every 4 or 6 h up to 24×10^6 U
≥0.1	≤0.5	Cefotaxime or ceftriaxone	200–225 mg every 6 or 8 h 100 mg every 12 or 24 h	2 g every 6 h 2 g every 12 h
	1.0	Cefotaxime or ceftriaxone plus vancomycin	300 mg every 6 or 8 h 100 mg every 12 or 24 h 60 mg every 6 h	300 mg[a] *(up to 24 g total)* 2 g every 12 h 60 mg[a] *every 6 h (up to 2 g total)*
	≥2.0	Same as for 1.0 μg/ml plus rifampin	20 mg every 12 h	300 mg every 12 h

[a] Doses are given as amounts per kilogram per day.

resistant to the extended-spectrum cephalosporins have been treated successfully with vancomycin alone or in combination with other antibiotics. Nevertheless, the efficacy of vancomycin in treating pneumococcal meningitis has been questioned by some investigators. Viladrich et al. (144) considered that four adults with pneumococcal meningitis treated with standard doses of vancomycin (7.5 mg/kg every 6 h) and with "recrudescence" of symptoms of meningitis had failed to respond to therapy; all the patients had an immediate clinical response after the antibiotic therapy was changed. Two of these patients had positive CSF cultures after 4 or 8 days of vancomycin treatment. The patients also received dexamethasone, 0.25 mg/kg, every 6 h for 4 days. One of the concerns was that dexamethasone may have altered penetration of the vancomycin into the CSF. However, in children, dexamethasone may not interfere with the penetration of vancomycin into CSF (82). In nine children with bacterial meningitis, the mean vancomycin level in CSF was 3.3 ± 1.1 μg/ml (range, 2 to 5.9 μg/ml) 2 to 3 h after a 15-mg/kg dose administered every 6 h for 24 to 48 h. They also were receiving dexamethasone at 0.6 mg/kg/day in four doses for 4 days. Although there was no control group not receiving dexamethasone, the penetration of vancomycin into the CSF was thought to be reliable. Similarly, ceftriaxone levels in CSF were not affected by dexamethasone therapy (57).

Based on these studies, some experts believe that if adjunctive dexamethasone is used, cefotaxime or ceftriaxone plus vancomycin remains suitable for children but rifampin plus ceftriaxone is the preferred regimen in adults, in whom dexamethasone administration may alter the penetration of vancomycin into the CSF (122). However, there are no human studies confirming these recommendations for adults.

Another approach to overcoming resistance is to increase the dose of certain antibiotics to achieve higher concentrations in the sera and subsequently in the CSF. Viladrich et al. (143) treated six patients with pneumococcal meningitis (seven episodes) caused by isolates with decreased susceptibility to cefotaxime (MIC = 1.0 μg/ml in five episodes and 2.0 μg/ml in two episodes). Cefotaxime was administered at a dose of 300 mg/kg/day with a maximum daily dose of 24 g. All patients experienced prompt clinical improvement.

The Committee on Infectious Diseases of the American Academy of Pediatrics has established guidelines for children with serious infections possibly caused by *S. pneumoniae* (34). For infants and children older than 1 month with suspected bacterial meningitis, the combination of cefotaxime or ceftriaxone and vancomycin should be administered initially. The recommended doses are as follows: cefotaxime, 225 to 300 mg/kg/day in three or four divided doses; ceftriaxone, 100 mg/kg/day in one or two divided doses; vancomycin, 60 mg/kg/day in four divided doses. Modification of therapy is based upon the isolate's susceptibility to penicillin and cefotaxime or ceftriaxone, and our recommendations are outlined in Table 2.

In addition to the clinical data by Viladrich et al. (143), two groups have measured the bactericidal activity of CSF following high-dose (300-mg/kg/day) cefotaxime therapy in children with bacterial meningitis. Friedland and Klugman (53) collected CSF at 2, 4, 6, or 8 h after a 100-mg/kg/dose administered every 8 h for 24 to 48 h. All the children also received dexamethasone (0.3 mg/kg every 12 h) intravenously. The bactericidal activity in CSF was measured against pneumococcal strains that were either susceptible, intermediate, or resistant (MIC = 4 μg/ml) to cefotaxime. Bactericidal activity was defined as greater than 99.9% killing of the inoculum. In 18 CSF specimens, bactericidal activity was detected in 17 (94%), 13 (72%), and 8 (44%) for the cefotaxime-susceptible, -intermediate, and -resistant strains, respectively. Only three of nine specimens obtained 6 to 8 h after infusion had bactericidal activity. Curiously, there was no correlation between the concentrations of cefotaxime or its metabolite, desacetyl-cefotaxime, in CSF and bactericidal activity. The authors concluded that in some patients the higher doses of cefotaxime still may not lead to sufficient bactericidal activity in CSF against pneumococcal strains intermediate to cefotaxime.

Doit et al. (42) conducted a similar study, except that children with bacterial meningitis were treated with cefotaxime (300 mg/kg/day in four divided doses) and vancomycin (60 mg/kg/day in four divided doses) without adjunctive dexamethasone. Bactericidal activity was defined as the highest dilution that killed 99.9% of the initial inoculum. The MIC of cefotaxime for the test pneumococcal strain was 1.0 μg/ml. CSF was obtained 2 h after at least the fifth infusion. The bactericidal titers in CSF were 1:16, 1:8, 1:4, 1:2, and <1:2 for one, four, seven, five, and two patients, respectively. The median concentration of cefotaxime or vancomycin in the CSF was 4.4 and 1.7 μg/ml, respectively. Again, there was no clear correlation between the concentrations of antibiotics in the CSF and the bactericidal titer; in many cases, much greater bactericidal activity was noted than would be predicted from the concentrations measured. This finding is consistent with at least additive activity between cefotaxime and vancomycin in vivo against *S. pneumoniae* (54).

The outcome of pneumococcal meningitis in children or adults has not been carefully assessed in the era of antibiotic-resistant strains and since the general recommendations for adding vancomycin routinely to extended-spectrum cephalosporins for initial empirical therapy have become routine. Arditi et al. (9) retrospectively evaluated 180 episodes of pneumococcal meningitis in children over a 3-year period in eight children's hospitals. Of the isolates, 13% were intermediate and 7% were resistant to penicillin; 7% were nonsusceptible to

ceftriaxone (2.8% were resistant). There were no bacteriologic treatment failures among the patients with isolates nonsusceptible to ceftriaxone. Fourteen patients died; none of the deaths were associated with documented bacteriological failure. The incidence of neurologic sequelae was no different for the patients with isolates nonsusceptible to ceftriaxone compared with those whose isolates were susceptible. Only five patients with isolates nonsusceptible to ceftriaxone received primary vancomycin therapy (two received meropenem).

The Centers for Disease Control and Prevention reported on the therapy and outcome of pneumococcal meningitis in three U.S. cities (Atlanta, Baltimore, and San Antonio) from November 1994 through April 1996 (99). A total of 110 cases were identified; 40% of the isolates were nonsusceptible to penicillin, and 15% were resistant. However, penicillin-nonsusceptible strains were not associated with excess mortality or a longer duration of hospitalization.

Newer Agents for Treating Meningitis due to Antibiotic-Resistant *S. pneumoniae*

Both cefepime, a broad-spectrum cephalosporin, and meropenem, a carbapenem antibiotic, have been evaluated in clinical trials for the treatment of bacterial meningitis. Cefepime has activity equivalent to cefotaxime or ceftriaxone against penicillin-resistant *S. pneumoniae*. Sáez-Llorens et al. (124) compared cefepime with cefotaxime in 90 children with bacterial meningitis. The mean concentrations of cefepime in CSF ranged from 3.3 to 5.7 μg/ml 0.5 to 8 h after a dose. Sequelae were equivalent between the two groups. However, no penicillin-resistant pneumococci were identified in the study, and so the effectiveness of cefepime for treating pneumococcal meningitis due to resistant strains could not be assessed and thus remains unknown.

Meropenem is approved for treating bacterial meningitis in infants, children, and adults. The in vitro activity of meropenem for penicillin-resistant *S. pneumoniae* is 1 to 2 dilutions higher than that of imipenem; the MIC at which 90% of the isolates are inhibited (MIC_{90}) is 0.5 μg/ml for penicillin-resistant strains. The activity against strains resistant to cefotaxime and ceftriaxone has not been well defined (118). Meropenem concentrations in CSF during meningitis range between 0.3 and 6.5 μg/ml after a 40-mg/kg dose, generally above the MIC_{90} for strains resistant to penicillin, suggesting that meropenem may be effective therapy (38). In vitro, the killing activity of meropenem at 3 μg/ml against 26 *S. pneumoniae* isolates was equivalent to that of ceftriaxone plus vancomycin at 8.8 μg/ml and 2.0 μg/ml, respectively. These are mean concentrations of the antibiotics in CSF after two doses (48). In one large multicenter trial involving 190 children with bacterial meningitis, 21 pneumococcal isolates were recovered; the cefotaxime MICs for 3 of the isolates were ≥0.5 μg/ml (84). Only one of these patients received meropenem. In ongoing studies of meningitis, a handful of other children with strains nonsusceptible to cefotaxime have received meropenem (25). Although meropenem is an alternative to extended-spectrum cephalosporins, much more experience with the drug is required before it can be recommended as an effective antibiotic for the treatment of antibiotic-resistant pneumococcal meningitis.

Trovafloxacin is one of the fluoroquinolones active in vitro against *S. pneumoniae*, including strains resistant to cefotaxime and ceftriaxone (17). Two studies of experimental meningitis in rabbits indicated that administration of trovafloxacin results in effective bactericidal activity in the CSF against penicillin- or cephalosporin-resistant pneumococci (80, 113). In children without meningeal inflammation, 22 to 30% of a concomitant level in serum is achieved in the CSF of children after treatment with alatrovafloxacin, the intravenous form of trovafloxacin (8). These levels are in excess of the concentrations of trovafloxacin needed to inhibit *S. pneumoniae* in vitro. Clinical studies may prove that trovafloxacin is an appropriate alternative agent for pneumococcal meningitis.

Dexamethasone

The use of adjunctive dexamethasone in addition to antibiotics for the treatment of pneumococcal meningitis remains somewhat controversial (127). The number of patients with pneumococcal meningitis enrolled in randomized trials of dexamethasone versus placebo was relatively small, and the timing of dexamethasone administration was not standardized in these studies. In two studies conducted in Turkey and Egypt, dexamethasone was associated with decreased hearing loss (66, 77). For the largest number of children with pneumococcal meningitis ($n = 33$) enrolled in a single study in the United States, bilateral hearing loss (3 of 11 children) was no different in the dexamethasone-treated children than in those receiving placebo (2 of 20) (147). However, this study has been criticized because dexamethasone was not given routinely just before or concomitant with the first dose of parenteral antibiotics. Nevertheless, in this study, dexamethasone was associated with a significant reduction in hearing loss for children with meningitis due to *Haemophilus influenzae* type b. In addition, inflammatory parameters were diminished to an equivalent degree in experimental pneumococcal meningitis when dexamethasone was administered 30 min before or 60 min after ampicillin treatment (89). In a retrospective analysis of children with pneumococcal meningitis, Arditi et al. (9) found no benefit with respect to hearing loss for children receiving dexamethasone either before or up to 1 h after the first dose of parenteral antibiotics compared with children never receiving any dexamethasone. A recent meta-analysis of randomized clinical trials of dexamethasone as adjunctive therapy in bacterial meningitis has concluded that "if commenced with or before parenteral antibiotics, (available evidence) suggests benefit for pneumococcal meningitis in childhood" (95).

The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that dexamethasone should be considered for the treatment of infants and children with pneumococcal meningitis (5). There are also uncertainties about the value of dexamethasone use in adults, and even fewer studies have been performed with adults than with children. Some experts recommend dexamethasone for adults with meningitis with a positive Gram stain of CSF (suggestive of a high concentration of bacteria in the CSF) and evidence of increased intracranial pressure (122).

Repeat Lumbar Puncture

For any patient who is not improving as expected or who has a pneumococcal isolate for which the cefotaxime or ceftriaxone MIC is ≥2.0 μg/ml, a repeat lumbar puncture 36 to 48 h after initiation of therapy is recommended to document sterility of the CSF. This is particularly crucial for patients who are receiving adjunctive dexamethasone therapy, since they may appear to be responding to antibiotic therapy with a decrease in fever despite the CSF remaining culture positive (44).

BACTEREMIA

The management of pneumococcal bacteremia due to antibiotic-resistant isolates is not as well formulated as it is for

TABLE 3. Pneumococcal bacteremia due to antibiotic-resistant isolates: therapy and outcome

Reference	Date of study	Age of patient	Underlying disorder	MIC (μg/ml) of:		Therapy[b]	Outcome
				Penicillin	Ceftriaxone		
Jackson et al. (75)	1984	12 mo	Otitis media	0.13–0.5		Penicillin G	Developed meningitis
		10 mo	Otitis media	0.13–0.5		Erythromycin-sulfisoxazole	Good
Schwartz et al. (129)	1991	9 mo	Otitis media	1.25		Ceftriaxone (2 doses), amox/clav[c]	Improved
		22 mo	Otitis media	0.125		Cefotaxime	Improved
Tan et al. (136)	1992	6 mo	Periorbital cellulitis	0.13		Cefuroxime (3)	Good[d]
		11 mo	Periorbital cellulitis	0.13		Cefuroxime (3), penicillin VK (7)	Good[d]
		11 mo	None	0.25		Amox/clav (10)	Good
		6 mo	None	0.25		Ceftriaxone (1 dose), amox/clav (10)	Good[d]
		6 mo	Buccal cellulitis	0.13		Ceftriaxone (1 dose), amox/clav (10)	Good[d]
		85 mo	HIV infection, premature	0.13		Cefuroxime (7) then oral cefuroxime (14)	Good[d]
		18 mo	Otitis media	0.25		Penicillin G (3), amox/clav (10)	Good[d]
		14 mo	None	0.25		Amox/clav (10)	Good
		18 mo	None	0.13		Ceftriaxone (1 dose), amoxicillin (10)	Good[d]
Leggiadro et al. (85)	1994	14 mo	NS[a]	8	4	Vancomycin	Curative
		14 mo	Cellulitis	4	1	Cefotaxime	Curative
		13 mo	Otitis media, sinusitis	4	4	Cefotaxime, oral erythromycin	Curative
Pikis et al. (117)	1995	16 mo	NS	0.13		Ceftriaxone (1 dose)	Good[d]
		15 mo	Otitis media	0.19		Amoxicillin (10)	Good[d]
		14 mo	NS	0.5		Ceftriaxone (2 doses)	Good[d]
		5 mo	Otitis media	2.0		Cefuroxime (7)	Good
Chesney et al. (33)	1995	16 mo	Sickle cell anemia	2.0	1	Ceftriaxone, vancomycin	Died 36 h later; blood culture negative at 8 h
		30 mo	Sickle cell anemia	0.12		NS	Good
		15 yr	Sickle cell anemia, renal transplant	0.12	0.25	NS	Good

[a] NS, not stated.
[b] Days of treatment given in parentheses.
[c] Amox/clav, amoxicillin-clavulanate.
[d] Repeat blood culture negative.

meningitis. Although pneumococcal bacteremia without a source is a relatively common invasive bacterial infection in children, only a few studies focusing on treatment outcome of infections due to isolates intermediate or resistant to penicillin or to cefotaxime and ceftriaxone have been performed. Table 3 compiles those cases from various reports that provide enough detail regarding treatment and outcome. For the majority of reported patients, resistance to penicillin is of the intermediate variety and the outcome of therapy certainly does not predict outcomes for patients whose isolates have greater resistance. Rarely have treatment failures been reported or documented for penicillin-nonsusceptible pneumococcal isolates. Breakthrough pneumococcal bacteremia and meningitis were documented in a normal 18-month-old child after receiving cefotaxime (180 mg/kg/day) for 2 days and subsequently receiving cefuroxime (200 mg/kg/day) for 4 days (27). The MICs of cefotaxime and cefuroxime for the isolated pneumococcus were 2.0 and 8.0 μg/ml, respectively.

In other studies, the outcome of bacteremia has been noted but details of therapy have not been provided. Oppenheim et al. (106) reported 16 children with penicillin-nonsusceptible pneumococcal bacteremia in 1983 from South Africa. The mortality in 35 children with bacteremia due to penicillin-susceptible *S. pneumoniae* was 28%, in contrast to 40% in the children infected with strains intermediate or resistant to penicillin; three of six patients with strains not susceptible to penicillin died when they received only penicillin or ampicillin. Welby et al. (148) reported seven children with pneumococcal bacteremia due to strains nonsusceptible to penicillin and at least one isolate for which the cefotaxime MIC was up to 1.0 μg/ml. All were treated with intravenous cefotaxime or ceftriaxone for at least 3 days and responded well. Friedland (51)

also described five children with pneumococcal bacteremia due to penicillin-intermediate isolates, all of whom had predisposing conditions and were initially treated with ampicillin. Two children died (one preterm infant died shortly after admission, and the second child had biliary atresia). In contrast, only 1 of 16 children (9 with predisposing conditions) with bacteremia due to penicillin-susceptible pneumococci died. None of these three studies mention the results of repeat blood cultures after antibiotics had been initiated.

One large study has examined the implications of penicillin resistance for pneumococcal bacteremia in adults (120). Of the patients in 10 adult care hospitals between January 1991 and April 1994, 590 had pneumococcal bacteremia. How many patients also may have had pneumonia was not stated. The mortality rate was similar for patients with infections due to penicillin-susceptible (19%) and penicillin-nonsusceptible (21%) isolates. However, among survivors, the duration of hospitalization was longer for the patients with nonsusceptible isolates (15.8 days; range, 1 to 46 days) than for those with susceptible isolates (12.1 days; range, 1 to 57 days) ($P = 0.05$). In another study of 184 adults with pneumococcal bacteremia, the risk of mortality also was not increased when an isolate was nonsusceptible to penicillin (79). In a study of invasive pneumococcal disease in patients with human immunodeficiency virus (HIV) infection, antibiotic susceptibility did not influence the outcome (49).

In eight children's hospitals over 36 months, more than 700 episodes of bacteremia without focus occurred in children (78). Management of patients was quite heterogeneous, but a single dose of ceftriaxone followed by an oral antibiotic was administered frequently as outpatient treatment. No patient was treated with penicillin only. Morbidity and mortality were not related to antibiotic susceptibility, and no microbiological treatment failures were encountered. Several children with an underlying illness had pneumococcal bacteremia due to penicillin-resistant isolates. These patients also were treated with a variety of regimens, none containing penicillin. Unfortunately, it is not possible to assess single-agent treatment in this group of patients who have predisposing conditions from this study. In a preliminary study, Silverstein et al. (131) at Children's Hospital in Boston reviewed the clinical presentation and outcome of children with pneumococcal bacteremia with respect to antimicrobial therapy. More than 700 children were included; 52 (7.2%) isolates were nonsusceptible to penicillin and 20 (2.8%) were nonsusceptible to ceftriaxone. Children with pneumococcal bacteremia due to isolates nonsusceptible to ceftriaxone were less likely than children with isolates susceptible to ceftriaxone to be described as improved by their families at follow-up (54.5 and 83.6%, respectively; $P = 0.03$) and experienced longer hospital stays (8.0 and 3.1 days, respectively; $P < 0.001$). Susceptibility to penicillin did not affect these parameters. Treatment failures were not addressed.

The magnitude of the peak level in serum and the duration of concentration higher than the MIC in serum that are required for an antibiotic to successfully treat pneumococcal bacteremia are not clear. Penicillin, cefuroxime, and cefotaxime or ceftriaxone achieve levels in the serum considerably greater than 2.0 μg/ml for several hours following standard doses; this level is considered resistant for these agents. Thus, even in the face of resistance, these antibiotics administered intravenously would be expected to result in clearance of pneumococcal bacteremia in a normal host. Whether this is also true for immunocompromised patients will have to be further documented as more clinical data are gathered. As clinical experience is gained with treating pneumococcal bacteremia due to antibiotic-resistant isolates, more solid recommendations can be made.

PNEUMONIA

As with bacteremia, it is difficult to determine the effect of antibiotic resistance on the outcome of pneumococcal pneumonia. Mortality can be compared, but this is an insensitive measure. Duration of hospitalization, oxygen administration, fever, and development of complications are other measures that can be compared. Eradication of bacteria from the bloodstream or pleural space is an objective microbiologic measure. However, for all of these factors, a number of confounding variables may influence the outcome measures. These include age, underlying disease, and duration and extent of illness at the start of treatment.

In early studies, investigators found that decreased penicillin susceptibility was associated with poorer responses to therapy. Jackson et al. (75) described two pediatric patients (6 weeks and 26 months old) who did not respond as expected to a beta-lactam antibiotic. Both had isolates (one from blood, one from the trachea) with intermediate susceptibility to penicillin, and they did not have a satisfactory response until erythromycin or vancomycin therapy was initiated. Feldman et al. (46) described three adults with community-acquired pneumococcal pneumonia due to strains intermediate (MIC = 0.5 μg/ml) or resistant (MIC = 2 or 4 μg/ml) to penicillin. All were initially treated with penicillin G (2×10^6 units every 4 to 6 h) and tobramycin. All the patients deteriorated, and two died, one within 24 h (24-year-old patients with systemic lupus erythematosus) and one within 72 h (36-year-old patient who was previously healthy). The third patient was a previously healthy 52-year-old individual, whose condition initially improved but who then died after 18 days despite treatment with vancomycin (500 mg every 6 h) and rifampin starting on the second hospital day. Repeat blood culture results were not mentioned.

Pallares et al. (108) reviewed the experience with bacteremic pneumococcal pneumonia in adult patients in Barcelona, Spain, from January 1981 to September 1986. Twenty-four patients had penicillin-nonsusceptible isolates (14 intermediate and 10 resistant, with penicillin MICs up to 8 μg/ml). Two control patients with bacteremic pneumonia due to penicillin-susceptible strains were matched to each pneumonia patient according to the nearest date of positive blood cultures. Thirteen patients (54%) and 12 controls (25%) died, most by the first 72 h of therapy ($P = 0.03$). The duration of fever in the survivors was equivalent. Of the 19 patients whose isolates had a penicillin MIC between 0.12 and 2.0 μg/ml, 11 recovered; all 9 not initially critically ill survived. Of 10 patients who received penicillin G and who had isolates for which the penicillin MICs were between 0.12 and 2.0 μg/ml, 6 survived. In addition, two patients with isolates for which the penicillin MICs were 4.0 or 8.0 μg/ml did not respond to penicillin therapy. The authors concluded that pneumonia due to pneumococcal strains for which the penicillin MICs were ≤2.0 μg/ml may be treated successfully with intravenous high-dose penicillin.

The same investigators reported an expanded experience with antibiotic-resistant pneumococcal pneumonia for the years 1984 through 1993 (109). Of the 504 adults with severe pneumococcal pneumonia (about 80% were bacteremic), 145 (29%) had penicillin-nonsusceptible strains and 31 (6%) had strains nonsusceptible to the extended-spectrum cephalosporins. Overall, the mortality rate for patients with penicillin-nonsusceptible strains was 38%, with respect to 24% for those with penicillin-susceptible strains ($P = 0.001$). However, when predictors of mortality (age 70 years or older, serious underlying disease, heart failure, shock, multilobar pneumonia, leukopenia, nosocomial pneumonia and polymicrobial pneumonia) were taken into account, there was no significant

difference in mortality between the groups. Similar results were found in 392 patients with monomicrobial bacteremic pneumococcal pneumonia. Among the patients treated with cefotaxime or ceftriaxone, mortality rates were similar for those infected with cephalosporin-susceptible (24%, $n = 168$) and those with cephalosporin-nonsusceptible (22%, $n = 18$) strains. No mention was made of repeat blood culture results. The authors again concluded that high-dose intravenous penicillin G (150,000 to 200,000 U/kg/day) "may be" effective for patients with pneumococcal pneumonia caused by strains nonsusceptible to penicillin (for which the penicillin MIC was <2.0 μg/ml). In addition, they proposed that ceftriaxone or cefotaxime may be a good alternative for strains for which the penicillin MICs exceeded 2.0 μg/ml but for which the cefotaxime or ceftriaxone MICs were <2.0 μg/ml.

A small number of children with pneumococcal pneumonia due to strains nonsusceptible to penicillin have been reported by several different investigators (117, 136, 148). In most cases, cefuroxime or an extended-spectrum cephalosporin was administered and was initially successful. When stated, repeat-blood cultures were negative and therapy was completed with an oral antibiotic. Most isolates showed intermediate susceptibility to penicillin.

Friedland (51) compared 25 children (16 with underlying diseases) having pneumonia due to *S. pneumoniae* with intermediate susceptibility to penicillin with 53 children (19 with underlying diseases) having pneumococcal pneumonia due to susceptible isolates. There were no significant differences between the groups in the duration of fever, respiratory distress, oxygen requirements, rates of improvement, or mortality (overall case fatality rate, 12%). A number of treatment regimens were used for the children with nonsusceptible strains. Four children were successfully treated only with amoxicillin orally. Fifteen children were treated initially with intravenous ampicillin ($n = 10$), penicillin ($n = 2$), or cefuroxime ($n = 3$). Twelve responded satisfactorily, and by day 2 or 4 of therapy they were switched to oral amoxicillin. Two patients died; both had HIV infection. Eight other children received an extended-spectrum cephalosporin with or without vancomycin; two of these children died. The author concluded that for non-central nervous system infections, pneumococcal isolates with intermediate susceptibility to penicillin have little clinical significance in pediatric patients.

In another report from Spain, Garcia-Leoni et al. (58) reviewed 139 patients of all ages with pneumococcal infection from January 1988 through October 1989. Pneumonia occurred in 89 patients; 53 (60%) were bacteremic, and 30 (11 had serious underlying illnesses) episodes were due to strains not susceptible to penicillin. Overall, there was no increase in mortality in patients infected with nonsusceptible strains. Fifteen patients with pneumococcal pneumonia died; four had strains with intermediate susceptibility, and one had a resistant isolate (penicillin MIC = 2.0 μg/ml). Four patients with nonsusceptible isolates received an extended-spectrum cephalosporin, and one received cloxacillin. For adults in Spain with cancer and neutropenia, the mortality related to pneumococcal pneumonia and bacteremia was not influenced by antibiotic susceptibility (31). Almost all of these patients were treated with ceftazidime or imipenem plus amikacin.

Sixteen episodes of pneumococcal pneumonia in HIV-infected inpatients were reported by Baril et al. (14) in France; 10 isolates were intermediate and 2 were resistant to penicillin. For the patients with strains with intermediate susceptibility to penicillin, five were treated with amoxicillin, one was treated with amoxicillin plus a fluoroquinolone, and four were treated with cefotaxime. Two treatment failures occurred; one in a patient given amoxicillin and the other in a patient given cefotaxime (100 mg/kg/day). Both patients with strains resistant to penicillin were treated successfully with cefotaxime or with vancomycin and amikacin.

Children with complicated parapneumonic effusions were compared for demographic and clinical features by Hardie et al. (70). Six children with infection due to *S. pneumoniae* not susceptible to penicillin were compared with 17 children whose isolates were susceptible to penicillin. The patients with nonsusceptible isolates were significantly younger (2.1 ± 0.6 and 7.9 ± 1.1 years, respectively; $P < 0.01$) and were more likely to have positive blood cultures (100 and 29%, respectively; $P < 0.05$). Five children in the nonsusceptible group underwent thoracoscopy or urokinase treatment, with respect to five in the susceptible group, but other features of the hospital course and outcome were no different between the groups.

Tan et al. (138) retrospectively evaluated more than 170 episodes of pneumococcal pneumonia in children seen at eight children's hospitals in the United States. A total of 75% of the children were hospitalized. Twenty-two patients (including 15 inpatients) had strains nonsusceptible to penicillin. The outcome was the same for those with strains nonsusceptible to penicillin as for those with penicillin-susceptible isolates. No conclusions could be drawn about specific therapy, since the antibiotic regimens used were so variable.

Trovafloxacin has excellent in vitro activity against *S. pneumoniae* isolates not susceptible to penicillin or extended-spectrum cephalosporins. In six separate clinical trials in adults with community-acquired pneumonia, 26 patients treated with oral or oral plus intravenous trovafloxacin had blood or sputum pneumococcal isolates nonsusceptible to penicillin; the clinical efficacy of this treatment for these patients was 96% (91). Thus, trovafloxacin also appears to be effective in treating community-acquired pneumonia due to *S. pneumoniae* isolates nonsusceptible to penicillin.

Levofloxacin, the active isomer of ofloxacin, has excellent in vitro activity against penicillin-nonsusceptible *S. pneumoniae* and is approved by the U.S. Food and Drug Administration for treatment of community-acquired pneumonia. In one study, levofloxacin was successful in eradicating *S. pneumoniae* with intermediate susceptibility to penicillin in six patients with pneumonia (47). Grepafloxacin has in vitro activity against antibiotic-resistant *S. pneumoniae*, but there are insufficient clinical data upon which to base any recommendations for its use for pneumonia due to penicillin-nonsusceptible *S. pneumoniae* (142).

Implications

Based on the above clinical studies in normal hosts, it appears that penicillin, ampicillin, or cefuroxime should be adequate to treat patients hospitalized with pneumonia due to pneumococcal isolates for which the penicillin MICs are ≤2.0 μg/ml. Oral therapy with amoxicillin, amoxicillin-clavulanate, or cefuroxime axetil also should be efficacious for initial outpatient management or when completing therapy once the patient has resolution of signs and symptoms following parenteral treatment. Although there are no specific studies, azithromycin should be efficacious for treating pneumonia due to susceptible isolates. For isolates for which the penicillin MICs are ≥4.0 μg/ml, alternate agents, including cefuroxime, cefotaxime, ceftriaxone, and clindamycin, if the isolates are susceptible, are suggested. For adults, trovafloxacin and possibly levofloxacin appear to be a reasonable choice in the inpatient or outpatient setting as well.

The Infectious Diseases Society of America has developed

guidelines for the management of community-acquired pneumonia in adults (20). The panel endorsed the use of parenteral penicillin G or oral amoxicillin as preferred agents for pneumococcal isolates susceptible to penicillin. Alternative agents such as vancomycin or fluoroquinolones or other agents active in vitro were preferred for strains resistant to penicillin (MIC $\geq$ 2.0 μg/ml). For strains with intermediate susceptibility to penicillin, parenteral penicillin or amoxicillin or the alternative agents were preferred.

The MICs of extended-spectrum cephalosporins above which treatment failure would be expected is not clear. Concentrations of cefotaxime and ceftriaxone in pleural fluid have been determined following doses of 1 g every 12 h and 1 g once daily, respectively, in adults with chest tubes placed for drainage of empyemas (126). The concentrations of cefotaxime or ceftriaxone reached approximately 10 μg/ml and exceeded 5.0 μg/ml for more than 5 h after the initial doses. One could expect to adequately treat pneumococcal pneumonia with cefotaxime or ceftriaxime when the extended-spectrum cephalosporins have an MIC of up to 4.0 μg/ml for the isolate, on the basis of this type of information. When the MICs are higher, alternate agents such as vancomycin, clindamycin, or a carbapenem may be needed. Additional studies are required before more specific recommendations can be made.

For critically ill patients or patients with an immunocompromising condition, consideration should be given to including vancomycin in the initial treatment regimen when *S. pneumoniae* is among the organisms requiring empirical coverage. Trovafloxacin is an alternative choice in adults. Modifications of therapy are then made based on antimicrobial susceptibility data as outlined above.

Animal models of pneumococcal pneumonia have been used to evaluate the efficacy of penicillin, extended-spectrum cephalosporins, carbapenems, vancomycin, and selected fluoroquinolones in the treatment of infection due to penicillin-resistant strains. Different conditions such as induction of leukopenia, use of a bacterial inoculum in agar, or infection of different species of rodents were used in these studies (13, 60, 97, 121, 125, 139). In general, higher doses of penicillin are superior to lower doses in clearing bacteria from the lungs and in decreasing the mortality. Cefotaxime and ceftriaxone typically are effective for strains susceptible or intermediate to these agents, although ceftriaxone appeared superior to cefotaxime in treating isolates resistant to extended-spectrum cephalosporin (MICs of 4 or 8 μg/ml) (125). Vancomycin and imipenem were the most active agents in one study. Sparfloxacin was more effective than ciprofloxacin or amoxicillin in decreasing mortality in a leukopenic-mouse model. These results also demonstrated that the time for which the antibiotic concentration in serum was above the MIC for the infecting strain of pneumococcus correlated with the outcome. These models help to confirm that the present approach to treatment of pneumococcal pneumonia due to antibiotic-resistant strains is reasonable and allow comparisons among new antibiotics for isolates with greater resistance to the traditional agents such as cefuroxime or the extended-spectrum cephalosporins.

MISCELLANEOUS INFECTIONS

Except for bacteremia and pneumonia, a limited number of other systemic non-central nervous system infections due to antibiotic-resistant *S. pneumoniae* have been reported, and most of these have occurred in children (Table 4). Infective endocarditis, aortitis, and endophthalmitis are other infections documented in single-case reports. Since a variety of antimicrobial regimens were used in these patients, it is very difficult to draw any conclusions regarding single-agent therapy. However, most of the antibiotics administered to these patients were shown to achieve concentrations in synovial fluid, peritoneal fluid, or bone in excess of their MICs for penicillin-resistant isolates (21, 26, 72, 98, 104, 123). In synovial fluid, ceftriaxone reaches a level of up to 66 to 100% of the concomitant levels in serum. Cefotaxime and ceftriaxone penetrate into peritoneal fluid at levels between 2 to 59 μg/ml, depending when the specimens are obtained after administration of a dose (50). The average vancomycin concentration in synovial fluid was 5.7 μg/ml (80% of the concomitant level in serum) in one study. In ascitic fluid, the average vancomycin level was 8.7 μg/ml (40% of the concomitant level in serum) (96) after multiple doses. Clindamycin reached levels of 2 to 3 μg/ml in either ascitic or synovial fluid, levels severalfold higher than the MICs for susceptible pneumococci (40). Thus, with standard doses of the extended-spectrum cephalosporins or clindamycin, successful treatment of peritonitis or septic arthritis due to penicillin-resistant *S. pneumoniae* would be anticipated. Vancomycin may be required for infections due to isolates with high-level resistance to these antibiotics. Some authors recommend adopting empirical therapy for pneumococcal endocarditis that parallels the therapy suggested for pneumococcal meningitis (extended-spectrum cephalosporin plus vancomycin) (10).

UPPER RESPIRATORY INFECTIONS

Of all the infections caused by *S. pneumoniae*, the most common are upper respiratory infections, especially otitis media and sinusitis. Since virtually all studies dealing with antibiotic-resistant *S. pneumoniae* have focused on acute otitis media, this section deals primarily with what has been described for middle ear infections. Presumably these data are also relevant for sinusitis.

Craig and Andes (35) have proposed that 80 to 85% efficacy in treating acute otitis media is achieved by commonly prescribed oral antibiotics when the concentrations of the drug in the middle ear exceed the MIC for the infecting bacteria for 40 to 50% of the dosing interval. By using these criteria, it is possible to predict which antibiotics are likely to be efficacious or poorly effective in the treatment of acute otitis media due to *S. pneumoniae* with decreased susceptibility to penicillin and other antibiotics. A comparison of recent MICs of common oral antibiotics (for more than 4,400 pneumococcal isolates from 92 laboratories across the United States in 1996 to 1997) and reported "peak" levels of antibiotic achieved in middle ear fluid is shown in Table 5 (93). Overall, 64% of the isolates were susceptible, 23% were intermediate, and 13% were resistant to penicillin. Since the levels in the middle ear are often achieved in patients with chronic otitis media undergoing pressure equalization tube placement, they may not reflect the levels achieved in patients with acute otitis media. Nevertheless, it is apparent that certain antibiotics would be expected to be more efficacious than others when treating pneumococcal otitis media due to resistant strains.

Trimethoprim-sulfamethoxazole does not penetrate into middle ear effusions adequately to predict efficacy for penicillin-intermediate isolates, since there is such considerable cross-resistance for this combination and penicillin. For clindamycin, the mean level in the middle ear mucosa is 3.6 μg/g. Whether this level correlates with those in middle ear effusion is not clear. Clindamycin remains quite active for most pneumococcal isolates resistant to penicillin and would be considered an alternative agent for treating otitis media caused by such

TABLE 4. Miscellaneous infections reported due to *S. pneumoniae* nonsusceptible to penicillin

Reference	Age of patient	Underlying illness	Infection syndrome	Penicillin MIC (μg/ml)	Therapy[b]	Outcome
Jackson et al. (75)	8 mo	NS[a]	Septic arthritis	Intermediate	Cefamandole and aminocillin; completed with oral chloramphenicol	Good
Tan et al. (136)	43 mo	Nephrotic syndrome	Peritonitis	0.125	Ampicillin i.v.[c] for 7 days	Good, afebrile within 24 h
	19 mo	Varicella	Septic arthritis	1.0	Nafcillin (4), penicillin (7) Cefotaxime (9), amoxicillin-clavulanate (10)	Good Afebrile after 8 days
Leggiadro et al. (85)	24 mo	NS	Orbital cellulitis and sinusitis	8.0	Vancomycin and cefotaxime; oral clindamycin and rifampin	Curative
Pikis et al. (117)	10 mo	NS	Septic arthritis	4.0	Oxacillin (3), cefotaxime (3), vancomycin (21)	Good
	3 mo	NS	Osteomyelitis	0.5	Oxacillin (3), cefotaxime (3), cefuroxime (8), cephalexin (21)	Good
Gelfand and Cleveland (64)	71 yr	None	Vertebral osteomyelitis	0.25	Ceftriaxone (28)	Good
Daum et al. (39)	4 yr	Choroid plexus carcinoma, bone marrow transplant	Epiglottitis	2.0	Vancomycin, ceftazidime	Good
Abbasi et al. (1)	20 mo	None	Septic arthritis and osteomyelitis	0.38	Nafcillin (4), vancomycin (2) Cefotaxime (2), penicillin G (10)	Good, afebrile after 24 h
	14 mo	None	Septic arthritis	1.5	Nafcillin (7), ceftriaxone (31) Vancomycin (28)	Good, afebrile after 72 h
	24 mo	None	Septic arthritis	8.0	Cefotaxime (6), nafcillin (3), vancomycin (19), rifampin (19), clindamycin (6)	Febrile for 21 days

[a] NS, not stated.
[b] Days of treatment given in parentheses.
[c] i.v., intravenous.

strains (103). In most areas, pneumococcal isolates resistant to macrolides generally remain susceptible to clindamycin.

Several studies have now reported the outcome of treating acute or persistent otitis media due to pneumococci that are nonsusceptible to penicillin (Table 6). As is generally the case, otoscopic evaluation of the tympanic membrane and clinical condition define the outcome measures. Thus, the results are somewhat subjective, especially in nonrandomized, investigator-unblinded studies. All the studies included an initial tympanocentesis for culture of middle ear fluid. Cefuroxime, cefprozil, and amoxicillin-clavulanate were found to be efficacious in most of the children evaluated in these studies; cefaclor and cefixime have not been as effective as some of these other agents. Although only a small number of children were treated in one study, cefpodoxime did not appear to be particularly effective despite having reasonable in vitro activity against *S. pneumoniae* isolates that are nonsusceptible to penicillin (43). This lack of effectiveness might possibly be related to the relatively low concentrations achieved in the middle ear. In a second study of cefpodoxime for otitis media, the outcome in all four children with penicillin-nonsusceptible strains (mainly intermediate) was satisfactory (61).

In several studies, a single intramuscular dose of ceftriaxone was comparable to a standard 10-day course of amoxicillin or trimethoprim-sulfamethoxazole for treatment of acute otitis media (15, 67). However, efficacy for antibiotic-resistant pneumococci was not assessed. In the gerbil model, a single 100-mg/kg dose of ceftriaxone was effective in treating otitis media due to *S. pneumoniae* strains resistant to penicillin and ceftriaxone (MIC of both antibiotics = 8.0 μg/ml) (18). Block et al. (23) found that 8 of 11 children with persistent otitis media responded to ceftriaxone (25 to 50 mg/kg/dose) administered once daily for 4 to 7 days. In a preliminary study, Leibovitz et al. (86) administered ceftriaxone (50 mg/kg once daily for 3 days) to children with acute otitis media that was nonresponsive to standard oral antibiotics. Tympanocentesis for middle ear cultures was performed on the day of enrollment and on days 4 to 10 and if clinical relapse occurred. Bacteriological eradication occurred in 9 of 9 patients with penicillin-susceptible pneumococcal isolates and in 27 of 31 patients (87%) with penicillin-intermediate isolates. Bacteriological relapse occurred in two children with isolates intermediate to penicillin. No pneumococcal isolates resistant to penicillin (MIC $\geq$ 2.0 μg/ml) were encountered. In a similar study, Gehanno et al. (62) recruited children who were considered clinical treatment failures for acute otitis media. Middle ear cultures were ob-

TABLE 5. Comparison of in vitro activity of oral antibiotics for *S. pneumoniae* isolates based on penicillin susceptibility and concentrations achieved in the middle ear

Antibiotic (reference)	Penicillin susceptible (μg/ml)		Penicillin intermediate (μg/ml)		Penicillin resistant (μg/ml)		Dose	Concn in middle ear (μg/ml)
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}		
Amoxicillin (130)	0.13	0.13	0.25	2.0	2.0	4.0	15 mg/kg	5.6
							1 g	6.2
							45 mg/kg	2–8
Cefaclor (103)	1.0	2.0	8.0	64	64	64	15–20 mg/kg	0.5–5.1
Cefixime (71)	0.25	0.5	4.0	16	32	64	8 mg/kg	1.3–1.5
Cefpodoxime (43)	0.13	0.13	0.5	2.0	4	8	4 mg/kg	0.9
Cefprozil (103)	0.25	0.25	1.0	8.0	16	32	15 mg/kg	2.0
Cefuroxime (144)	0.13	0.13	0.5	4.0	4.0	8.0	15 mg/kg	1.4
Loracarbef (103)	1.0	2.0	8.0	64	64	64	15 mg/kg	3.9
Azithromycin (103)	0.13	0.13	0.13	8.0	1	64	10 mg/kg	8.6
							10 mg/kg then 5 mg/kg	9.4
Erythromycin (103, 140)	0.12	0.12	0.12	16	0.12	>16	15 mg/kg	4.5
Clarithromycin (103)	0.13	0.13	0.13	2.0	0.5	64	7.5 mg/kg	2.5
Ceftriaxone (68, 78)		0.06		1.0		2.0	50 mg/kg	35
Trimethoprim-sulfamethoxazole (103, 140)	0.25	>4.0	>4.0	>4.0	4.0	4.0	4 mg/kg	1.4–2.0

tained, and treatment with ceftriaxone (50 mg/kg) once daily for 3 days was administered. Thirty-six children had *S. pneumoniae* isolates for which the penicillin MICs were ≥1 μg/ml. One day after ceftriaxone therapy was completed, 24 of 27 had negative repeat cultures of the middle ear. Clinical successes were found for 88% of the patient on days 10 to 12 after enrollment and for 64% on days 28 to 42. Together, these two studies establish ceftriaxone as an important alternative agent for the treatment of acute otitis media unresponsive to first-line agents. However, three intramuscular doses probably are required, and the treatment is expensive.

Clindamycin and azithromycin have not been evaluated adequately to assess their role in the treatment of pneumococcal otitis media. Block et al. (23) reported anecdotal experience for seven children. In studies conducted in Israel, azithromycin was effective if the middle ear pneumococcal isolate was susceptible to azithromycin (eradicated in 12 of 12 patients) but totally ineffective when the isolate was azithromycin resistant (eradicated in 0 of 6 patients) (37). In a chinchilla model of acute otitis media, penicillin-resistant pneumococci remaining susceptible to clarithromycin were eradicated from middle ear cultures following clarithromycin treatment (4). Taken together, data from these studies suggest that the macrolides may provide effective therapy for treatment of acute otitis media due to penicillin-nonsusceptible strains remaining susceptible to the macrolides. However, since more than half of the pneumococcal isolates nonsusceptible to penicillin will be nonsusceptible to macrolides, it is not likely that azithromycin or clarithromycin will be highly effective in treating acute otitis media due to such strains (140).

Another approach has been to increase the dose of amoxicillin for the treatment of acute otitis media in order to in-

TABLE 6. Outcome of treatment for otitis media due to *S. pneumoniae*: effect of penicillin susceptibility

Location (reference)	Antibiotics	Dose mg/kg/day	No. of patients with successful clinical outcome/total no. infected		
			Penicillin susceptible	Penicillin intermediate	Penicillin resistant
France (63)	Cefuroxime axetil	30	39/42	9/10	24/32
Kentucky (23)	Ceftriaxone			3/5	5/6
	Amoxicillin-clavulanate			8/10	2/2
	Clindamycin			2/3	2/4
	Cefixime			1/5	0/3
	Cefpodoxime			1/3	2/5
	Cefaclor			1/2	1/4
United States (multicenter) (74)	Amoxicillin-clavulanate	40 and 10	56/63	7/8	7/9
Israel (36, 37)[a]	Cefuroxime axetil	30	20/22	15/19	
	Cefaclor	40	24/25	5/12	
	Amoxicillin	50	10/10	10/14	
	Cefaclor	40	13/16	6/17	
United States (multicenter) (115)	Cefprozil	40	39/50	11/12	21/31

[a] Bacteriological cure on day 4 to 5 of therapy by second tympanocentesis culture.

crease the concentration of amoxicillin in serum and thus the level in the middle ear fluid. In the chinchilla model, an amoxicillin dose 10-fold greater than that necessary to eradicate penicillin-susceptible strains was effective in clearing penicillin-resistant *S. pneumoniae* from the middle ear (19). In children with acute otitis media, levels of amoxicillin in middle ear fluid exceeded 1.0 μg/ml in most and exceeded 4.0 μg/ml in some after a single 45-mg/kg dose (130). In another study of acute otitis media in children, middle ear fluid was obtained after the children had received amoxicillin at 40 mg/kg/day every 8 h for 48 to 72 h and then a single 25-mg/kg oral dose of amoxicillin (30). The estimated mean peak concentration in middle ear fluid occurred 3.0 h after this oral dose and was ~9.5 μg/ml. About 60% of the levels were ≥2.0 μg/ml between 2.3 and 4.7 hours after the 25-mg/kg oral dose. The authors concluded that about 90% of episodes of pneumococcal acute otitis media could be treated effectively with an amoxicillin dosing regimen of 75 mg/kg/day in three divided doses. Using double the recommended dose of amoxicillin (80 mg/kg/day), Block et al. (23) successfully treated two patients with otitis media due to penicillin-resistant pneumococci. If the MIC_{90} of amoxicillin is 4.0 μg/ml for penicillin-resistant *S. pneumoniae*, levels exceeding this concentration can be achieved in middle ear fluid in many patients with the double dose of amoxicillin.

Implications

It is unclear if treatment failures for acute otitis media are occurring more frequently now than 10 years ago in association with the rise in the incidence of antibiotic-resistant *S. pneumoniae*. Pichichero and Pichichero (116) estimated that approximately 10% of visits for acute otitis media by children seen in one large private practice in Rochester, N.Y., were for persistent acute otitis media (i.e., infection that had failed one or two consecutive courses of antibiotics) for the period October 1989 through September 1992. Most of these children were 6 to 36 months old. Tympanocentesis was performed in 137 children whose acute otitis media had not responded after one or two empirical antimicrobial treatment courses. No pathogen was isolated from almost 50% of children, and *S. pneumoniae* was recovered from 24%. Only one-third of the isolates were tested for penicillin susceptibility; 2 of 11 were nonsusceptible to penicillin. Thus, at least during this period, treatment failures of acute otitis media were not often a result of *S. pneumoniae* isolates resistant to commonly prescribed antibiotics. However, similar data from 1997 to 1998 are not available, and these presumably would show higher rates of antimicrobial resistance among *S. pneumoniae* isolates, especially for isolates recovered from the upper respiratory tract, to determine if penicillin-resistant *S. pneumoniae* are now more commonly associated with treatment failures of acute otitis media.

Amoxicillin is still considered the agent of choice in treating acute otitis media. Certain risk factors have been identified as associated with an increased likelihood of treatment failure: a history of recurrent otitis media and treatment during the winter months are two of the strongest (23). Younger age and day care attendance might be considered additional risk features. Modifying this initial approach would be reasonable when faced with a younger child with these risk factors. One suggestion is to use an increased dose of amoxicillin (60 to 80 mg/kg/day) for routine first-line therapy in children who are not toxic with moderately severe acute otitis media. This higher dose does not appear to be associated with any greater adverse effect than does the standard 40-mg/kg/day dose. If a child is nonresponsive to this higher dosing level of amoxicillin, alternative agents to consider include amoxicillin-clavulanate, cefuroxime axetil, and cefprozil. Parenteral administration of ceftriaxone for at least three consecutive days is another option (23, 62, 86).

ANTIBIOTICS IN DEVELOPMENT

After a period when relatively few new antibiotics were introduced, the emergence of strains of antibiotic-resistant bacteria has spurred research into new antimicrobial compounds. Some of the preparations belong to unique antimicrobial classes, while others represent refinements of older antibiotics. Those that are being tested and appear useful against *S. pneumoniae*, especially penicillin- and macrolide/azolide-resistant strains, are discussed below, and the in vitro activities of the compounds are presented in Table 7.

Streptogramins

The streptogramins are inhibitors of cell wall synthesis at the ribosomal level and have been used in Europe since 1955. They are active against most gram-positive bacteria, including all pneumococcal strains, regardless of penicillin or macrolide susceptibility. RP 59500 (Synercid) is a 30:70 semisynthetic injectable combination of quinupristin and dalfopristin. Separately, these agents are active but bacteristatic for pneumococci, while the combination has synergistic activity and is rapidly bactericidal for all pneumococci (22, 110). RPR 106972 is a combination of two streptogramins (RPR 112808 and RPR 106950) and represents an oral preparation similar to Synercid. RP 7293 (Pyostacine), a single oral streptogramin that has been licensed in France and Belgium for more than 20 years, is very active against strains of *S. pneumoniae* (110).

Cephalosporins

Cefditoren is a pivaloyloxymethyl ester of the parent cephalosporin molecule and is intended for oral treatment (134). This antimicrobial agent is inhibitory and bactericidal at concentrations between 0.008 and 1.0 μg/ml and showed no inoculum effect when studies were repeated with higher inocula.

Trinems

Sanfetrinem (GV104326) is a tricyclic β-lactam (trinem) structurally similar to the carbapenems (132). Pharmacokinetic studies in human volunteers found maximum levels of sanfetrinem in serum of 2.5 μg/ml. Based on these findings, predicted levels in serum would exceed the MIC_{90} for between 20 and 40% of a 12-h dosing interval. Preliminary studies in children with acute otitis media following 10 mg/kg doses of sanfetrinem cilexetil twice a day have found about 40% (range, 13 to 81%) penetration into middle ear fluid (87). These levels suggest this agent should be effective in treating acute otitis media in pediatric patients.

Glycopeptides

LY 333328 is a semisynthetic glycopeptide that is active against vancomycin-resistant enterococci and other gram-positive bacteria, including *S. pneumoniae* (45). It is highly protein bound but rapidly bactericidal against both pneumococci and enterococci.

Fluoroquinolones

Sparfloxacin has a structure similar to clinafloxacin (65). Trovafloxacin is a novel fluoroquinolone with enhanced activ-

TABLE 7. In vitro activity of new antibiotics against *S. pneumoniae*

Antibiotic (no. of strains tested)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	Reference
Streptogramins				
RP59500 (Quinupristin/Dalfopristin) (Synercid)				110
Penicillin susceptible (4)	0.5	0.5	0.5	
Penicillin intermediate (2)	0.25	0.5	0.25–0.5	
Penicillin resistant (4)	0.5	1.0	0.5–1.0	
RPR 106972				135
Penicillin susceptible (75)	0.03	0.125	0.016–0.5	
Penicillin intermediate (55)	0.125	0.5	0.016–0.5	
Penicillin resistant (73)	0.25	0.5	0.016–0.5	
RPR 106972				135
Erythromycin resistant, clindamycin susceptible (143)	0.125	0.5	0.016–0.5	
Erythromycin resistant, clindamycin resistant (60)	0.125	0.25	0.016–0.5	
RP 7293				110
Penicillin susceptible (4)	0.125	0.25	0.125–0.25	
Penicillin intermediate (2)	0.125	0.125	0.125	
Penicillin resistant (4)	0.25	0.25	0.125–0.25	
Cephalosporin				
Cefditoren				135
Penicillin susceptible (75)	≤0.06	≤0.06	<0.06	
Trimen				
GV104325 (Sanfetrinem)				41
Penicillin susceptible (1167)	0.015	0.015	0.004–0.25	
Penicillin intermediate (216)	≤0.06	0.5	0.008–1.0	
Penicillin resistant (145)	0.5	1.0	0.12–2.0	
Glycopeptide				
LY333328				45
Penicillin susceptible (51)	0.002	0.008	0.002–0.06	
Penicillin intermediate (75)	0.002	0.008	0.002–0.06	
Penicillin resistant (76)	0.005	0.03	0.002–0.125	
Fluoroquinolone				
Levofloxacin				119
Penicillin susceptible (460)	1.0	2.0	0.05–4.0	
Penicillin intermediate (34)	1.0	2.0	0.05–4.0	
Penicillin resistant (5)	1.0	2.0	0.05–4.0	
Levofloxacin				145
Penicillin susceptible (3)	1.0	2.0	1.0–2.0	
Penicillin intermediate (3)	1.0	2.0	1.0–2.0	
Penicillin resistant (3)	1.0	4.0	1.0–4.0	
Sparfloxacin				16
Erythromycin, >256 μg/ml (21)	0.5	1.0	0.25–1.0	
Erythromycin, 4–64 μg/ml (29)	0.5	1.0	0.25–1.0	
Sparfloxacin				145
Penicillin susceptible (3)	0.25	0.25	0.25	
Penicillin intermediate (3)	0.25	0.25	0.25	
Penicillin resistant (3)	0.5	0.5	0.25–0.5	
Grepafloxacin				111
Penicillin intermediate (71)	0.25	0.5	0.125–1.0	
Penicillin resistant (58)	0.25	0.5	0.125–1.0	
DU-6859a				145
Penicillin susceptible (3)	0.064	0.064	0.064	
Penicillin intermediate (3)	0.064	0.064	0.064	
Penicillin resistant (3)	0.064	0.064	0.064	

Continued on following page

TABLE 7—*Continued*

Antibiotic (no. of strains tested)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	Reference
Bay 12-8039				146
Penicillin susceptible (53)	0.125	0.25		
Penicillin intermediate (45)	0.125	0.25		
Penicillin resistant (45)	0.125	0.25		
Sparfloxacin				105
Penicillin nonsusceptible (28)	0.06	0.12	0.03–0.25	
Oxazolidinones				
Linezolid				92
Penicillin intermediate (162)	0.5	1.0	0.06–2.0	
Penicillin resistant (68)	1.0	1.0	0.25–4.0	
Eperezolid				92
Penicillin intermediate (162)	0.25	0.25	0.06–1.0	
Penicillin resistant (68)	0.25	0.5	0.125–1.0	
Rifamycins				56
Penicillin susceptibility unknown (20)	0.0039	0.0313	0.0005–0.25	

ity for gram-positive bacteria over the earlier quinolones (105). Trovafloxacin may be the first quinolone actually studied in children for possible licensure. Experiments involving a rabbit model of meningitis showed that pretreatment of pneumococci with trovafloxacin delayed the release of the cytokines tumor necrosis factor and interleukin-1β compared to ceftriaxone. DU-6859a is probably the most active of the newer fluoroquinolones in vitro (111). Nine strains of pneumococci, for which the MICs of cefotaxime were 2 μg/ml or greater, were associated with uniform DU-6859a MICs of 0.064 μg/ml (145). BAY 12-8039 is an experimental oral broad-spectrum 8-methoxyquinolone (146). With a dosage of 400 mg/day, levels of 3.2 μg/ml in serum, with a half life of 12 h, were obtained in adults.

Oxazolidinones

The oxazolidinones, represented by Linezolid (U-100766) and Eperezolid (U-100592), are a new class of antimicrobial agent with a unique structure and good activity against gram-positive bacteria (92). Studies with penicillin and ceftriaxone non susceptible *S. pneumoniae* found that Eperezolid was more active in vitro; however, Linezolid is now in phase II and phase III trials. Both compounds inhibit bacterial protein synthesis and are bactericidal for pneumococci but not for other gram-positive organisms.

Rifabutin

Rifabutin is a lipophilic antibacterial that inhibits DNA-dependent RNA polymerase and is rapidly bactericidal for many bacteria, including *S. pneumoniae* (56). Penicillin-intermediate strains were inhibited by concentrations between 0.008 and 0.015 μg/ml. In a rabbit model of meningitis, rifabutin at 5 mg/kg/h was as effective as ceftriaxone at 10 mg/kg/h and rifabutin inhibited the release of tumor necrosis factor alpha (128).

CONCLUSIONS

The management of infection due to antibiotic-resistant *S. pneumoniae* is in flux, and it is likely that approaches to antimicrobial treatment will be modified as susceptibility patterns change. Unless there is a dramatic change in the antibiotic-prescribing habits of physicians and other health care workers, it is unlikely that the upward trend in antibiotic resistance will be halted. A number of organizations, especially the Centers for Disease Control and Prevention, are initiating efforts to educate health care workers and the public about the proper and wise use of antibiotics. Different dosing schemes of available agents and discovery of newer agents with different mechanisms of action remain important approaches to the development of new strategies for treating these infections. Perhaps the development of conjugate pneumococcal vaccines provides the greatest promise for controlling antibiotic-resistant *S. pneumoniae* by preventing this infection to a great degree.

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